REMARKS

Claims 22-23, 25-28, 30-31, 33, and 36-44 are pending. Claims 22 and 33 are amended to delete the reference to a transgenic "rodent" and now refer to a transgenic "mouse." Claim 22 is also amended to incorporate the limitations of claim 24 (which has now been canceled). Claims 22 and 33 have been amended further to recite the induction of toxicological stress to cause expression of the tagged reporter gene. New claims 36-44 have been added to refer to a transgenic "rat" as further described below. No new matter is believed to be added by the present amendments. Applicants have canceled claims 24 and 32-35.

Below is a detailed summary of the invention followed by a response to the final office action.

The invention, as now more particularly claimed, is directed to a method of detecting, screening for, or monitoring of toxicological stress in a transgenic mouse or rat. The cells of the transgenic mouse or rat express a peptide-tagged beta-lactoglobulin protein as a reporter gene. When the transgenic mouse or rat is subjected to toxicological stress as called for in the methods of this invention, the expression of a tagged beta-lactoglobulin reporter gene is detected, screened for or monitored. This allows the investigation of modified gene expression in a wide range of areas in which changes in gene expression plays a role. Thus, the invention is used to analyze changes in gene expression in response to specific stimuli caused by toxicological stress.

Based on the amendments, we have more precisely defined "gene activation event" as expression of a peptide tagged beta-lactoglobulin reporter gene in response to toxicological stress, have claimed a more narrow group of non-human animals, mice and rats, and have limited the invention to the method of detecting toxicological stress in such ways as to enable any person having skill in the arts to make and use the invention. Applicants therefore ask that the rejections be reconsidered and withdrawn.

Page numbers, as used herein, refer to publication number WO 2004/011676 A2.

1. Objection to the Specification

The disclosure was objected to because pages 8 and 16 contained an embedded hyperlink and/or other form of browser-executable code.

The MPEP provides examples of "embedded hyperlinks and/or other forms of browser executable code" as follows: "Examples of a hyperlink or a browser-executable code are [1] a URL placed between these symbols "< >" and [2] http:// *followed by* a URL address." (MPEP § 608.01 VII, emphasis added).

The hyperlink on page 8 (www.ncbi.nlm.nih.gov) has been amended to remove the embedded hyperlink, leaving only the text "www.ncbi.nlm.nih.gov." The browser-executable code on page 16 (http://www.ncbi.nlm.nih.gov) has been amended to remove "http://" leaving only the URL address so that it reads "www.ncbi.nlm.nih.gov." The drawing descriptions for Figures 20 and 22 on page 37 have been amended to remove the embedded hyperlinks (www.ncbi.nlm.nih.gov/entrz) so that each reads "www.ncbi.nlm.nih.gov/entrz."

Since the amendments to the specification remove the hyperlink, Applicants request that this objection be withdrawn.

2. Claim Rejection: 35 U.S.C. § 112, First Paragraph, Written Description

In order to expedite prosecution, and for that reason alone, claims 22, 33, and 34 have been amended to recite "mouse" instead of "rodent." Support for this amendment can be found throughout the specification on page 25 at line 11 (host cells are transfected with a nucleic acid construct where the cell type may be mouse hepatoma epithelial cells), page 25 at line 30 (the preferred transgenic animal is a mouse), and page 32 line 13 (the method of detecting the activation of a reporter gene employs a fertilized mouse egg or a transfected mouse ES cell line).

New claims 36-44 have also been added. These claims are directed to methods of detecting, screening for and monitoring of toxicologically induced stress in a transgenic rat by detecting gene expression of a peptide tagged beta-lactoglobulin reporter gene. Support for these claims can be

found throughout the specification such as page 25 line 32 (the transgenic animal may be a rat) and page 37 (an example disclosing the cDNA sequence encoding the mRNA of rat alpha-2-u globulin).

These claims now define a method of detecting, screening for, or monitoring of toxicologically induced stress in a transgenic mouse or rat.

Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

3. Claim Rejection: 35 U.S.C. § 112, First Paragraph, Enablement

Claims 22-28 and 30-33 were rejected for failing to comply with the written description requirement. This rejection is based on the use of the term "transgenic rodent" in the claims. Applicants respectfully submit that an invention claiming transgenic mice and rats is sufficiently narrow to overcome the U.S.C. § 112, first paragraph, rejection and that the description indeed enables one skilled in the art to be in possession of the invention.

To expedite prosecution, and for that reason alone, claims 22 and 33 have been amended to recite "mouse" instead of "rodent." Support for these amendments can be found throughout the specification on page 25 at line 11 (host cells are transfected with a nucleic acid construct where the cell type may be mouse hepatoma epithelial cells), page 25 at line 30 (the preferred transgenic animal is a mouse), and page 32 line 13 (the method of detecting the activation of a reporter gene employs a fertilized mouse egg or transfected mouse ES cell line).

The specification teaches the method detecting the activation of a reporter gene as a result of exposure to toxicological stress in a mouse cell *in vivo*, according to claim 22, beginning on page 32 of the application. Additionally, the specification teaches the method of monitoring toxicologically induced stress in a transgenic mouse or rodent, according to claim 33, on page 27 and page 49 at the first full paragraph. Finally, examples are also provided on pages 38-49.

New claims 36-44 have been added and are directed to methods of detecting induced stress in a cell *in vivo* in rats. Support for this amendment can be found throughout the specification such as page 25, line 32, (the transgenic animal may be a rat) and page 37 (an example disclosing the cDNA sequence encoding the mRNA of rat alpha-2-μ globulin).

The specification teaches the method detecting toxicologically induced stress in a transgenic rat *in vivo*, according to claim 36, beginning on page 32 of the application. Additionally, the specification teaches the method of monitoring toxicologically induced stress in a transgenic rat, according to claim 46, on page 27 and page 49 at the first full paragraph. Finally, examples are also provided on pages 38-49.

Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

In view of the above amendments, the teachings in the specification, and the previously submitted Declaration of Dr. Bruce Whitelaw, Applicants believe the claims are in condition for allowance.

Please charge the $810.00 fee for the Request for Continued Examination of this application. No other fees are believed to be due with this response. However, if an additional fee is due, please charge our Deposit Account No. 08-0219, under Order No. 0102286.00155US1 from which the undersigned is authorized to draw.

Respectfully submitted,

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